

# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## **SUMMARY OF SAFETY AND EFFECTIVENESS**

### **I. GENERAL INFORMATION**

Device Generic Name: Prosthesis, Intervertebral Disc

Device Trade Name: CHARITÉ Artificial Disc

Applicant's Name and Address: DePuy Spine, Inc.  
A Johnson & Johnson Company  
325 Paramount Drive  
Raynham, MA 02767

Date(s) of Panel Recommendation: June 2, 2004

Premarket Approval Application (PMA) Number: P040006

Date of Notice of Approval to Applicant: October 26, 2004

### **II. INDICATIONS FOR USE**

The CHARITÉ Artificial Disc is indicated for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have no more than 3mm of spondylolisthesis at the involved level. Patients receiving the CHARITÉ Artificial Disc should have failed at least six months of conservative treatment prior to implantation of the CHARITÉ Artificial Disc.

### **III. CONTRAINDICATIONS**

The CHARITÉ Artificial Disc should not be implanted in patients with the following conditions:

- Active systemic infection or infection localized to the site of implantation
- Osteoporosis
- Osteopenia
- Bony lumbar stenosis
- Allergy or sensitivity to implant materials
- Isolated radicular compression syndromes, especially due to disc herniation
- Pars defect

#### IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CHARITÉ Artificial Disc labeling.

#### V. DEVICE DESCRIPTION

The CHARITÉ Artificial Disc is a weight-bearing modular implant consisting of two endplates and one sliding core. Endplates are manufactured from cobalt-chromium alloy and are available in various sizes and degrees of angulation (parallel and oblique). A parallel and an oblique endplate of the same size can be combined for adaptation to the patient's lumbar lordosis. The sliding cores are manufactured from ultra-high molecular weight polyethylene (UHMWPE) with a radiopaque cobalt-chromium alloy wire for x-ray visualization. The sliding cores are available in various thicknesses with sizing consistent with endplate sizing.

As shown in **Table 1**, the endplates are available in five sizes, each of which is available in four shapes to conform to the individual patient's lumbar lordosis: plane-parallel (zero degree) and oblique (angled at 5°, 7.5°, or 10°). As detailed in **Table 2**, the UHMWPE core is available in five heights for sizes 1 through 3 and in four heights for sizes 4 and 5. The core also incorporates a circumferential radio-opaque cobalt/chromium alloy wire for x-ray visualization.

| <b>Table 1 CHARITÉ Endplates</b> |                          |                               |                         |
|----------------------------------|--------------------------|-------------------------------|-------------------------|
| <b>Size</b>                      | <b>Dimensions</b>        |                               | <b>Angles Available</b> |
|                                  | <b>AP width<br/>(mm)</b> | <b>Lateral width<br/>(mm)</b> |                         |
| 1                                | 23                       | 28.5                          | 0, 5, 7.5, 10           |
| 2                                | 25                       | 31.5                          | 0, 5, 7.5, 10           |
| 3                                | 27                       | 35.5                          | 0, 5, 7.5, 10           |
| 4                                | 29                       | 38.5                          | 0, 5, 7.5, 10           |
| 5                                | 31                       | 42.0                          | 0, 5, 7.5, 10           |

| <b>Table 2 CHARITÉ Cores</b> |                          |                                   |
|------------------------------|--------------------------|-----------------------------------|
| <b>Size</b>                  | <b>Diameter<br/>(mm)</b> | <b>Heights Available<br/>(mm)</b> |
|                              |                          |                                   |
| 1                            | 23                       | 7.5, 8.5, 9.5, 10.5, 11.5         |
| 2                            | 25                       | 7.5, 8.5, 9.5, 10.5, 11.5         |
| 3                            | 27                       | 7.5, 8.5, 9.5, 10.5, 11.5         |
| 4                            | 29                       | 8.5, 9.5, 10.5, 11.5              |
| 5                            | 31                       | 8.5, 9.5, 10.5, 11.5              |

#### VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-surgical alternatives to performing disc replacement in the lumbar vertebral region include, but are not limited to, conservative treatment without intervention, medications, chiropractic care, disc injections, and/or physical therapy.

Surgical alternatives include, but are not limited to, surgical decompression, posterior lumbar interbody fusion (PLIF) procedures with or without posterior instrumentation, anterior lumbar interbody fusion (ALIF) procedures with or without posterior instrumentation and combined anterior and posterolateral (360°) fusion procedures, fusions using anterior/anterolateral spinal systems (e.g., plate and screw systems) or fusions using posterior spinal systems (e.g., pedicle screw/rod and hook/rod systems). In each case, the fusions would involve the use of autograft and/or allograft bone.

## VII. MARKETING HISTORY

The CHARITÉ Artificial Disc has been commercially available in markets outside of the United States since 1987. A listing of countries marketing the device is included below in **Table 3**. The device has not been withdrawn from the market for any reason. Distribution within the United States has been restricted to use in the IDE study only.

| <b>Table 3 Use of CHARITÉ Disc in Other Countries</b> |                |
|---|----------------|
| Australia   | Italy          |
| Austria   | Malaysia       |
| Belgium   | México         |
| Brazil  | New Zealand    |
| Canada  | Portugal       |
| Chile   | Slovenia       |
| China   | South Africa   |
| Denmark   | South Korea    |
| Egypt   | Spain          |
| France  | Switzerland    |
| Germany   | United Kingdom |
| Israel  | United States  |
|   | Venezuela      |

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The CHARITÉ Artificial Disc was implanted in 205 investigational subjects and compared to 99 control subjects who received a commercially available spinal fusion cage filled with iliac crest autograft. Each investigational site was also required to enroll their first five CHARITÉ Artificial Disc subjects as training cases with a total of 71 training subjects enrolled. The treatment and control groups were implanted with the devices via an anterior surgical approach.

Adverse event (AE) rates presented are based on the number of subjects having at least one occurrence for a particular adverse event divided by the total number of randomized subjects in that treatment group. Table 4a presents AEs that occurred in > 1% of Charité subjects.

**Table 4a Adverse Events – Pivotal Study**

| Complication  | Intraoperative<br>0-2 days |         | Perioperative<br>>2 days - 42 days |         | Short Term<br>>42 days - 210 days |         | Long Term<br>>210 days |         | # of Subjects Reporting & Total<br>Adverse Events* |  |
|---|----------------------------|---------|------------------------------------|---------|-----------------------------------|---------|------------------------|---------|--|--|
|   | Inves.                     | Control | Inves.                             | Control | Inves.                            | Control | Inves.                 | Control | Investigational #<br>(% of 205) total<br>events    | Control<br># (% of 99)<br>total events |
| Burning or dysesthetic pain                           | 0                          | 2       | 3                                  | 0       | 2                                 | 1       | 0                      | 0       | 5 (2.4)<br>5                                       | 3 (3.0)<br>3                           |
| Cardiovascular  | 5                          | 0       | 1                                  | 1       | 0                                 | 0       | 0                      | 0       | 6 (2.9)<br>6                                       | 1 (1.0)<br>1                           |
| Clinically significant blood loss (> 1500 cc)         | 1                          | 2       | 0                                  | 0       | 0                                 | 0       | 0                      | 0       | 1 (0.5)<br>1                                       | 2 (2.0)<br>2                           |
| Collapse/subsidence into adjacent vertebrae           | 1                          | 0       | 2                                  | 0       | 1                                 | 0       | 3                      | 1       | 7 (3.4)<br>7                                       | 1 (1.0)<br>1                           |
| Dermatological  | 2                          | 3       | 1                                  | 0       | 0                                 | 0       | 0                      | 0       | 3 (1.5)<br>3                                       | 3 (3.0)<br>3                           |
| Dizziness   | 2                          | 0       | 2                                  | 0       | 0                                 | 0       | 0                      | 0       | 4 (2.0)<br>4                                       | 0 (0.0)<br>0                           |
| Drug allergy  | 0                          | 0       | 1                                  | 2       | 0                                 | 0       | 0                      | 0       | 1 (0.5)<br>1                                       | 2 (2.0)<br>2                           |
| Edema   | 1                          | 1       | 2                                  | 0       | 1                                 | 2       | 1                      | 0       | 5 (2.4)<br>5                                       | 3 (3.0)<br>3                           |
| Fever   | 3                          | 6       | 0                                  | 2       | 0                                 | 0       | 0                      | 0       | 3 (1.5)<br>3                                       | 8 (8.1)<br>8                           |
| Fracture (non-vertebral)                              | 0                          | 0       | 0                                  | 0       | 2                                 | 1       | 2                      | 0       | 5 (2.4)<br>4*                                      | 1 (1.0)<br>1                           |
| Gastrointestinal                                      | 7                          | 3       | 4                                  | 3       | 1                                 | 0       | 0                      | 1       | 13 (6.3)<br>12*                                    | 7 (7.1)<br>7                           |
| Genitourinary   | 1                          | 1       | 0                                  | 0       | 1                                 | 0       | 2                      | 0       | 4 (2.0)<br>4                                       | 1 (1.0)<br>1                           |
| Hernia  | 0                          | 0       | 0                                  | 1       | 1                                 | 0       | 0                      | 1       | 1 (0.5)<br>1                                       | 2 (2.0)<br>2                           |
| Infection – other non-wound related                   | 1                          | 0       | 1                                  | 0       | 1                                 | 0       | 2                      | 1       | 5 (2.4)<br>5                                       | 1 (1.0)<br>1                           |
| Infection – Superficial wound with incision site pain | 0                          | 1       | 9                                  | 1       | 2                                 | 0       | 2                      | 0       | 13 (6.3)<br>13                                     | 2 (2.0)<br>2                           |
| Infection – UTI                                       | 1                          | 0       | 2                                  | 1       | 2                                 | 0       | 0                      | 0       | 5 (2.4)<br>5                                       | 1 (1.0)<br>1                           |
| Motor deficit in index level                          | 1                          | 0       | 0                                  | 0       | 1                                 | 1       | 1                      | 0       | 3 (1.5)<br>3                                       | 1 (1.0)<br>1                           |
| Musculoskeletal                                       | 1                          | 0       | 1                                  | 0       | 1                                 | 0       | 1                      | 1       | 4 (2.0)<br>4                                       | 1 (1.0)<br>1                           |
| Musculoskeletal spasms – back                         | 1                          | 0       | 3                                  | 1       | 3                                 | 1       | 1                      | 0       | 8 (3.9)<br>8                                       | 2 (2.0)<br>2                           |
| Musculoskeletal spasms – back and leg                 | 1                          | 0       | 2                                  | 0       | 1                                 | 1       | 1                      | 0       | 5 (2.4)<br>5                                       | 1 (1.0)<br>1                           |
| Musculoskeletal spasms – leg                          | 0                          | 0       | 4                                  | 0       | 3                                 | 1       | 0                      | 0       | 7 (3.4)<br>7                                       | 1 (1.0)<br>1                           |
| Numbness index level related                          | 2                          | 2       | 9                                  | 4       | 7                                 | 0       | 2                      | 1       | 20 (9.8)<br>20                                     | 7 (7.1)<br>7                           |
| Numbness peripheral nerve or non-index level related  | 2                          | 0       | 0                                  | 3       | 3                                 | 0       | 0                      | 1       | 5 (2.4)<br>5                                       | 4 (4.0)<br>4                           |
| Other   | 2                          | 1       | 1                                  | 1       | 2                                 | 1       | 0                      | 0       | 5 (2.4)<br>5                                       | 3 (3.0)<br>3                           |
| Pain – back   | 2                          | 3       | 12                                 | 11      | 27                                | 16      | 15                     | 2       | 59 (28.8)<br>56*                                   | 32 (32.3)<br>32                        |
| Pain – back and lower extremities                     | 1                          | 1       | 9                                  | 4       | 10                                | 7       | 5                      | 2       | 25 (12.2)<br>25                                    | 14 (14.1)<br>14                        |
| Pain – back and other                                 | 1                          | 0       | 0                                  | 0       | 1                                 | 0       | 0                      | 0       | 3 (1.5)<br>2*                                      | 0 (0.0)<br>0                           |
| Pain – incision site                                  | 4                          | 1       | 2                                  | 0       | 0                                 | 0       | 0                      | 0       | 6 (2.9)<br>6                                       | 1 (1.0)<br>1                           |
| Pain – lower extremities                              | 9                          | 2       | 28                                 | 10      | 16                                | 9       | 9                      | 4       | 63 (30.7)<br>62*                                   | 25 (25.3)<br>25                        |
| Pain – lower extremities with numbness at index level | 0                          | 0       | 3                                  | 1       | 0                                 | 1       | 1                      | 1       | 4 (2.0)<br>4                                       | 4 (4.0)<br>3*                          |
| Pain other (not back/hip/leg)                         | 5                          | 1       | 2                                  | 1       | 8                                 | 3       | 5                      | 3       | 21 (10.2)<br>20*                                   | 8 (8.1)<br>8                           |
| Psychological   | 0                          | 0       | 1                                  | 0       | 1                                 | 2       | 1                      | 1       | 3 (1.5)<br>3                                       | 3 (3.0)<br>3                           |
| Reflex change   | 0                          | 0       | 0                                  | 0       | 2                                 | 1       | 0                      | 1       | 2 (1.0)<br>2                                       | 2 (2.0)<br>2                           |

**Table 4a Adverse Events – Pivotal Study**

| Complication                  | Intraoperative<br>0-2 days |         | Perioperative<br>>2 days - 42 days |         | Short Term<br>>42 days - 210 days |         | Long Term<br>>210 days |         | # of Subjects Reporting & Total<br>Adverse Events* |  |
|-------------------------------|----------------------------|---------|------------------------------------|---------|-----------------------------------|---------|------------------------|---------|--|--|
|                               | Inves.                     | Control | Inves.                             | Control | Inves.                            | Control | Inves.                 | Control | Investigational #<br>(% of 205) total<br>events    | Control<br># (% of 99)<br>total events |
| Respiratory                   | 3                          | 1       | 0                                  | 0       | 0                                 | 0       | 0                      | 0       | 3 (1.5)<br>3                                       | 1 (1.0)<br>1                           |
| Retrograde ejaculation        | 2                          | 2       | 0                                  | 0       | 1                                 | 1       | 0                      | 0       | 3 (1.5)<br>3                                       | 3 (3.0)<br>3                           |
| Surgery – index level         | 1                          | 0       | 0                                  | 0       | 1                                 | 2       | 8                      | 6       | 11 (5.4)<br>10*                                    | 8 (8.1)<br>8                           |
| Vessel damage/bleeding, minor | 7                          | 0       | 0                                  | 0       | 1                                 | 1       | 0                      | 0       | 8 (3.9)<br>8                                       | 1 (1.0)<br>1                           |
| Any Adverse Event             |                            |         |                                    |         |                                   |         |                        |         | 155 (75.6)   | 77 (77.8)                              |

\*In cases where the totals in this column do not correspond with additions from timecourse columns to the left, the sponsor has data that documents that an adverse event occurred, but does not have data to specify the time frame. The numbers in these columns represent the total adverse events reported in the study.

<sup>1</sup>Five randomized CHARITÉ subjects reported seven "Other" events: twitching head and hand, nosebleeds, peritoneal tear, nausea, fainting, syncope, and flu.

<sup>2</sup>Three control subjects reported three "Other" events: arachnoiditis, lip blister, and whole body swelling.

The incidence of the following adverse events occurred in 1% or less of the total investigational group subjects: adjacent level DDD or DJD changes, anemia, annulus ossification, calcification resulting in bridging trabecular bone, coumadin overdose, dermatological drug allergy, dural tear, epidural hematoma, fatigue, groin pain, headache, herniated nucleus pulposus, ileus requiring N/G tube, implant displacement, incontinence, insomnia, IV site inflammation, major vessel damage/bleeding, narcotic addiction, nerve root injury, non-specific musculoskeletal spasms, other degenerative lumbar disease, peritoneal adhesions, positive Waddell signs, pulmonary embolism, pulmonary infection, puritis, retroperitoneal hematoma, spinal stenosis, spondylolisthesis acquisita, surgery unrelated to the lumbar spine, thrombosis, and wound swelling infection. One death related to narcotics use was reported.

The following table compares the complications that occurred in >1% of the 71 training patients with the complications that occurred in >1% of the 205 randomized subjects.

**Table 4b Adverse Events – CHARITÉ Randomized vs Training Cases**

| Complication                                   | Intraoperative<br>0-2 days |        | Perioperative<br>>2 - 42 days |        | Short Term<br>>42 - 210 days |        | Long Term<br>>210 days |        | # of Subjects Reporting & Total<br>Adverse Events* |  |
|--|----------------------------|--------|-------------------------------|--------|------------------------------|--------|------------------------|--------|--|--|
|  | Rand.                      | Train. | Rand.                         | Train. | Rand.                        | Train. | Rand.                  | Train. | Randomized #<br>(% of 205)<br>Total events         | Training#<br>(% of 71)<br>Total events |
| Anemia   | 1                          | 1      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 2 (<1)<br>1*                                       | 1 (1.4)<br>1                           |
| Annular Ossification                           | 0                          | 0      | 0                             | 0      | 0                            | 0      | 1                      | 1      | 1 (<1)<br>1  | 1 (1.4)<br>1                           |
| Bowel Perforation                              | 0                          | 1      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 0  | 1 (1.4)<br>1                           |
| Burning or dysesthetic pain                    | 0                          | 0      | 3                             | 0      | 2                            | 2      | 0                      | 1      | 5 (2.4)<br>5                                       | 3 (4.2)<br>3                           |
| Cardiovascular                                 | 5                          | 0      | 1                             | 1      | 0                            | 0      | 0                      | 0      | 6 (2.9)<br>6                                       | 1 (1.4)<br>1                           |
| Clinically significant blood loss (> 1500 cc)  | 1                          | 0      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 1 (<1)<br>1  | 0                                      |
| Collapse/subsidence into adjacent vertebrae    | 1                          | 0      | 2                             | 0      | 1                            | 0      | 3                      | 0      | 7 (3.4)<br>7                                       | 0                                      |
| Degenerative Disease Progression, other lumbar | 1                          | 0      | 0                             | 0      | 0                            | 0      | 0                      | 1      | 1 (<1)<br>1  | 1 (1.4)<br>1                           |
| Degenerative Disease Progression, non-lumbar   | 0                          | 0      | 0                             | 0      | 0                            | 1      | 0                      | 1      | 0  | 2 (2.8)<br>2                           |
| Dermatological                                 | 2                          | 2      | 1                             | 0      | 0                            | 0      | 0                      | 0      | 3 (1.5)<br>3                                       | 2 (2.8)<br>2                           |

**Table 4b Adverse Events – CHARITÉ Randomized vs Training Cases**

| Complication  | Intraoperative<br>0-2 days |        | Perioperative<br>>2 - 42 days |        | Short Term<br>>42 - 210 days |        | Long Term<br>>210 days |        | # of Subjects Reporting & Total<br>Adverse Events* |  |
|---|----------------------------|--------|-------------------------------|--------|------------------------------|--------|------------------------|--------|--|--|
|   | Rand.                      | Train. | Rand.                         | Train. | Rand.                        | Train. | Rand.                  | Train. | Randomized #<br>(% of 205)<br>Total events         | Training#<br>(% of 71)<br>Total events |
| Diplopia  | 0                          | 1      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 0  | 1 (1.4)<br>1                           |
| Dizziness   | 2                          | 1      | 2                             | 0      | 0                            | 0      | 0                      | 0      | 4 (2.0)<br>4                                       | 1 (1.4)<br>1                           |
| Edema   | 1                          | 2      | 2                             | 1      | 1                            | 0      | 1                      | 0      | 5 (2.4)<br>5                                       | 3 (4.2)<br>3                           |
| Fever   | 3                          | 3      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 3 (1.5)<br>3                                       | 3 (4.2)<br>3                           |
| Fracture (non-vertebral)  | 0                          | 0      | 0                             | 0      | 2                            | 0      | 2                      | 1      | 5 (2.4)<br>4*                                      | 1 (1.4)<br>1                           |
| Gastrointestinal  | 7                          | 8      | 4                             | 2      | 1                            | 0      | 0                      | 1      | 13 (6.3)<br>12*                                    | 11 (15.5)<br>11                        |
| Genitourinary   | 1                          | 0      | 0                             | 0      | 1                            | 1      | 2                      | 1      | 4 (2.0)<br>4                                       | 2 (2.8)<br>2                           |
| Headache  | 0                          | 1      | 0                             | 0      | 1                            | 0      | 0                      | 0      | 1 (<1)<br>1  | 1 (1.4)<br>1                           |
| Hernia  | 0                          | 0      | 0                             | 0      | 1                            | 1      | 0                      | 1      | 1 (<1)<br>1  | 2 (2.8)<br>2                           |
| Ileus requiring N/G tube  | 1                          | 2      | 1                             | 1      | 0                            | 0      | 0                      | 0      | 2 (<1)<br>2  | 3 (4.2)<br>3                           |
| Implant displacement  | 1                          | 1      | 0                             | 2      | 0                            | 1      | 0                      | 0      | 1 (<1)<br>1  | 4 (5.6)<br>4                           |
| Infection -- other non-wound related                            | 1                          | 0      | 1                             | 1      | 1                            | 2      | 2                      | 1      | 5 (2.4)<br>5                                       | 4 (5.6)<br>4                           |
| Infection -- Peritonitis  | 0                          | 0      | 0                             | 1      | 0                            | 0      | 0                      | 0      | 0  | 1 (1.4)<br>1                           |
| Infection -- Superficial wound with incision site pain          | 0                          | 1      | 9                             | 4      | 2                            | 0      | 2                      | 0      | 13 (6.3)<br>13                                     | 5 (7.0)<br>5                           |
| Infection -- UTI  | 1                          | 0      | 2                             | 1      | 2                            | 0      | 0                      | 0      | 5 (2.4)<br>5                                       | 1 (1.4)<br>1                           |
| Insomnia  | 0                          | 0      | 0                             | 1      | 1                            | 0      | 0                      | 0      | 1 (<1)<br>1  | 1 (1.4)<br>1                           |
| Motor deficit in index level                                    | 1                          | 0      | 0                             | 1      | 1                            | 0      | 1                      | 0      | 3 (1.5)<br>3                                       | 1 (1.4)<br>1                           |
| Musculoskeletal   | 1                          | 0      | 1                             | 1      | 1                            | 0      | 1                      | 1      | 4 (2.0)<br>4                                       | 2 (2.8)<br>2                           |
| Musculoskeletal spasms -- back                                  | 1                          | 0      | 3                             | 1      | 3                            | 1      | 1                      | 1      | 8 (3.9)<br>8                                       | 3 (4.2)<br>3                           |
| Musculoskeletal spasms -- back and leg                          | 1                          | 0      | 2                             | 0      | 1                            | 0      | 1                      | 0      | 5 (2.4)<br>5                                       | 0                                      |
| Musculoskeletal spasms -- leg                                   | 0                          | 0      | 4                             | 2      | 3                            | 1      | 0                      | 0      | 7 (3.4)<br>7                                       | 3 (4.2)<br>3                           |
| Numbness and motor deficit index level                          | 0                          | 1      | 0                             | 1      | 0                            | 0      | 0                      | 0      | 0  | 2 (2.8)<br>2                           |
| Numbness index level related                                    | 2                          | 3      | 9                             | 4      | 7                            | 5      | 2                      | 2      | 20 (9.8)<br>20                                     | 14 (19.7)<br>14                        |
| Numbness lower sacral root distribution                         | 0                          | 0      | 0                             | 1      | 0                            | 1      | 0                      | 0      | 0  | 2 (2.8)<br>2                           |
| Numbness peripheral nerve or non-index level related            | 2                          | 2      | 0                             | 0      | 3                            | 1      | 0                      | 0      | 5 (2.4)<br>5                                       | 3 (4.2)<br>3                           |
| Other   | 2                          | 2      | 1                             | 0      | 2                            | 1      | 0                      | 1      | 5 (2.4) <sup>1</sup><br>5                          | 4 (5.6) <sup>2</sup><br>4              |
| Pain -- back  | 2                          | 3      | 12                            | 6      | 27                           | 15     | 15                     | 3      | 59 (28.8)<br>56*                                   | 27 (38.0)<br>27                        |
| Pain -- back and lower extremities                              | 1                          | 1      | 9                             | 2      | 10                           | 3      | 5                      | 2      | 24 (11.7)<br>25                                    | 8 (11.3)<br>8                          |
| Pain -- back and lower extremities with burning                 | 1                          | 0      | 1                             | 0      | 0                            | 0      | 0                      | 1      | 2 (<1)<br>2  | 1 (1.4)<br>1                           |
| Pain -- back and lower extremities with numbness at index level | 0                          | 0      | 0                             | 0      | 0                            | 0      | 0                      | 1      | 0  | 1 (1.4)<br>1                           |
| Pain -- back and other  | 1                          | 1      | 0                             | 0      | 1                            | 0      | 0                      | 0      | 3 (1.5)<br>2*                                      | 1 (1.4)<br>1                           |
| Pain -- groin area  | 1                          | 0      | 0                             | 2      | 0                            | 0      | 0                      | 0      | 1 (<1)<br>1  | 2 (2.8)<br>2                           |

| <b>Table 4b Adverse Events – CHARITÉ Randomized vs Training Cases</b> |                            |        |                               |        |                              |        |                        |        |  |  |
|---|----------------------------|--------|-------------------------------|--------|------------------------------|--------|------------------------|--------|--|--|
| Complication  | Intraoperative<br>0-2 days |        | Perioperative<br>>2 - 42 days |        | Short Term<br>>42 - 210 days |        | Long Term<br>>210 days |        | # of Subjects Reporting & Total<br>Adverse Events* |  |
|   | Rand.                      | Train. | Rand.                         | Train. | Rand.                        | Train. | Rand.                  | Train. | Randomized #<br>(% of 205)<br>Total events         | Training#<br>(% of 71)<br>Total events |
| Pain – incision site  | 4                          | 8      | 2                             | 1      | 0                            | 0      | 0                      | 0      | 6 (2.9)<br>6                                       | 9 (12.7)<br>9                          |
| Pain – lower extremities  | 9                          | 3      | 28                            | 7      | 16                           | 10     | 9                      | 1      | 63 (30.7)<br>62*                                   | 21 (29.6)<br>21                        |
| Pain – lower extremities and incision site                            | 0                          | 2      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 0  | 2 (2.8)<br>2                           |
| Pain – lower extremities with numbness at index level                 | 0                          | 0      | 3                             | 1      | 0                            | 0      | 1                      | 0      | 4 (2.0)<br>4                                       | 1 (1.4)<br>1                           |
| Pain other (not back/hip/leg)   | 5                          | 3      | 2                             | 2      | 8                            | 2      | 5                      | 4      | 21 (10.2)<br>20*                                   | 11 (15.5)<br>11                        |
| Psychological   | 0                          | 0      | 1                             | 0      | 1                            | 1      | 1                      | 0      | 3 (1.5)<br>3                                       | 1 (1.4)<br>1                           |
| Reflex change   | 0                          | 0      | 0                             | 0      | 2                            | 1      | 0                      | 0      | 2 (<1)<br>2  | 1 (1.4)<br>1                           |
| Respiratory   | 3                          | 0      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 3 (1.5)<br>3                                       | 0                                      |
| Retrograde ejaculation  | 2                          | 0      | 0                             | 0      | 1                            | 0      | 0                      | 0      | 3 (1.5)<br>3                                       | 0                                      |
| Seizures  | 0                          | 1      | 0                             | 0      | 0                            | 0      | 0                      | 0      | 0  | 1 (1.4)<br>1                           |
| Surgery – index level   | 1                          | 2      | 0                             | 1      | 1                            | 0      | 8                      | 2      | 11 (5.4)<br>10*                                    | 5 (7.0)                                |
| Thrombosis (DVT leg)  | 0                          | 0      | 0                             | 1      | 0                            | 0      | 0                      | 0      | 0  | 1 (1.4)<br>1                           |
| Vessel damage/bleeding, minor   | 7                          | 4      | 0                             | 0      | 1                            | 0      | 0                      | 0      | 8 (3.9)<br>8                                       | 4 (5.6)<br>4                           |
| Any Adverse Event   |                            |        |                               |        |                              |        |                        |        | 155 (75.6)   | 64 (90.1)                              |

\*In cases where the totals in this column do not correspond with additions from timecourse columns to the left, the sponsor has data that documents that an adverse event occurred, but does not have data to specify the time frame. The numbers in these columns represent the total adverse events reported in the study.

<sup>1</sup>Five randomized CHARITÉ subjects reported seven "Other" events: twitching head and hand, nosebleeds, peritoneal tear, nausea, fainting, syncope, and flu.

<sup>2</sup>Four training CHARITÉ subjects reported five "Other" events: multiple sclerosis, stiffness, left earache, bilateral eye redness, and vertigo.

Adverse events considered by the investigators to be device-related, including back and lower extremities pain, implant displacement, and subsidence, were greater in the investigational group (16/205, 7.8%) compared to the control group (4/99, 4.0%).

Device failures were those that required reoperation, revision, removal, or supplemental fixation. Device failures occurred in 11/205 (5.4%) CHARITÉ Artificial Disc and 8/99 (8.1%) control subjects. The majority of these events were supplemental fixation: 9/205 (4.4%) CHARITÉ Artificial Disc subjects and 6/99 (6.1%) of control subjects. Two (1.0%) CHARITÉ Artificial Disc subjects required removal of their implant.

| <b>Table 5 Adverse Events – CHARITÉ Randomized vs Training Cases</b> |                         |                      |
|--|-------------------------|----------------------|
|  | Randomized # (% of 205) | Training # (% of 99) |
| <b>Device-related adverse events</b>                                 | <b>16 (7.8%)</b>        | <b>4 (4.0)</b>       |
| Pain, back   | 5 (2.4%)                | 1 (1.0)              |
| Pain, back and lower extremities                                     | 5 (2.4%)                | 1 (1.0)              |
| Pain, lower extremities  | 2 (<1.0)                | 0 (0.0)              |
| Nerve root injury  | 1 (<1.0)                | 0 (0.0)              |
| Collapse, subsidence   | 1 (<1.0)                | 0 (0.0)              |

|                       |          |         |
|-----------------------|----------|---------|
| Implant displacement  | 1 (<1.0) | 0 (0.0) |
| Removal of prosthesis | 1 (<1.0) | 0 (0.0) |

There were two adverse events which occurred in the control group that were not present in the CHARITÉ Artificial Disc subjects. 18/205 subjects (18.2%) experienced pain at the donor graft site, and 9/99 (9.1%) experienced pseudoarthrosis.

The incidence of adverse events within the first 2 days of surgery was higher among training subjects (33/71, 46.5%) than among randomized CHARITÉ Artificial Disc subjects (58/205, 28.3%). The rates at all other time periods are similar between these two groups. There was a higher incidence of device-related adverse events in the training group (8/71, 11.3%) than in the randomized CHARITÉ Artificial Disc group (16/205, 7.8%).

**Potential Adverse Events:**

The following potential adverse events (singly or in combination) which might be expected to occur, but were not observed in the clinical trial, could also result from the implantation of the CHARITÉ Artificial Disc:

- Mechanical failure of the device due to bending or breakage resulting in loss of disc height
- Expulsion or retropulsion, potentially causing pain, paralysis, vascular or neurologic damage, spinal cord impingement or damage, or other conditions
- Implant breakage
- Reoperation due to mechanical breakdown of the device or if the implantation procedure fails to resolve the patient's syndrome
- Change in lordosis
- Injury to kidneys or ureters
- Deterioration in neurologic status
- Facet joint deterioration
- Spondylolysis
- Spondylolistheses
- Nerve damage due to surgical trauma or presence of the device, neurological difficulties including bowel and/or bladder dysfunction, impotence, tethering of nerves in scar tissue, muscle weakness or paraesthesia

- Vascular damage resulting in catastrophic or fatal bleeding
- Malpositioned implants adjacent to large arteries or veins could erode these vessels and cause catastrophic bleeding in the late postoperative period
- Dural tears experienced during surgery resulting in the need for further surgery for dural repair, a chronic CSF leak or fistula, and possible meningitis
- Bursitis
- Paralysis
- Reflex sympathetic dystrophy
- Damage to lymphatic vessels and/or lymphatic fluid exudation
- Fracture of bony structures
- Death

## **IX. SUMMARY OF PRECLINICAL STUDIES**

Biomechanical experiments were conducted to characterize the performance of the CHARITÉ Artificial Disc under static and dynamic loads.

### **Mechanical Testing**

Mechanical testing of the CHARITÉ Artificial Disc was conducted to evaluate the biomechanical properties of the device. All mechanical testing used cores of 7.5 mm thickness, which are the thinnest available sizes. This represents a worst-case scenario, since these cores provide the least material and therefore the highest stress concentrations. Some tests also involved 9.5 mm cores to further characterize the implants.

### **Static Testing**

Biomechanical experiments were conducted to characterize the performance of the device under static loads, including evaluations of the following:

- compressive strength and displacement (ultimate, yield, and bending) with and without flexion/extension
- creep
- range of motion
- stiffness

Summary data for these evaluations are listed in **Table 6**.

| <b>Test</b> | <b>Test Description</b>   | <b>Test Samples</b>  | <b>Method</b>  | <b>Results</b>   |
|-------------|---|--|--|--|
| 1           | Preliminary Test of Compressive Strength                          | Twenty 7.5 mm cores: ten with parallel and ten with oblique endplates.   | Axial compression to failure, with eccentric /off-axis loading onto the outer rim of the core.   | Deformation did not exceed 50%.<br><br>Ultimate Strength (kN):<br><ul style="list-style-type: none"> <li>Parallel = <math>7.55 \pm 2.75</math></li> <li>Off-axis loading on outer rim = <math>1.37 \pm 0.06</math></li> </ul>  |
| 2           | Preliminary Test of Bending Compressive Strength                  | Twenty 7.5 mm cores: ten with parallel and ten with oblique endplates.   | Bending compression to failure, with eccentric loading onto the outer rim of the core.   | Ultimate Strength (kN):<br><ul style="list-style-type: none"> <li>Parallel = <math>2.32 \pm 0.05</math></li> <li>Off-axis loading on outer rim = <math>2.36 \pm 0.16</math></li> </ul>   |
| 3           | Creep   | Nine 7.5 mm cores with parallel endplates.   | 50 hours of max load followed by 48 hours with no load; samples in 37°C water bath; at least 2 samples tested at each load, which was 1, 2, 3, or 4 kN.  | Max initial height deformation (immediately after 50 hours of load) = 7.6%. (0.57 mm)<br><br>Max height deformation after relaxation = 2.3 % (0.17 mm)   |
| 4           | Range of Motion   | Eight cadaveric spines (L2-S1) with L4-5 reconstructions using CHARITÉ disc, interbody fusion cage, and interbody fusion cage with a pedicle screw system. | $\pm 8$ Nm moment applied to produce flexion-extension, lateral bending, and axial rotation movements; intact spine compared to the reconstructed spines for ROM distribution from L3-S1 and for location of center of rotation. | CHARITÉ reconstructed specimens exhibited 3% increase in flexion/extension, 16% increase in lateral bending, and 44% compared to intact specimens<br><br>Mean segmental translation:<br>CHARITÉ = $2.06 \pm 0.77$ mm<br>Intact = $1.9 \pm 0.98$ mm<br><br>Centers of rotation were in the posterior 1/3 of the operative and adjacent intervertebral discs for the CHARITÉ reconstruction and intact specimens |
| 5           | Supplemental Test of Axial Compression with Flexion and Extension | Thirty 7.5 mm cores & thirty 9.5 mm cores; 15 of each core used with parallel endplates and 15 used with oblique endplates.                                | Implant tested at neutral (0°), max flexion (13.5°) and max extension (7.5°).  | Min yield @ 0° = $16.38 \pm 0.29$ kN<br>Min yield @ 13.5° = $4.899 \pm 0.345$ kN<br>Min yield @ 7.5° = $16.58 \pm 1.67$ kN<br><br>Max deformation = 9-20% after 50-60% recovery.   |

The preliminary compressive strength tests (Tests #1 and #2) revealed that eccentric, or off-axis, loading of the core occurred in flexion and extension displacements of greater than 32 degrees, which caused the periphery of the cores to become the primary load-bearing surface instead of the center of the core. Because the expected *in vivo* range of motion of the device in flexion/extension is expected to be between 0 and 21 degrees, the observed worst case ultimate loads may not be indicative of the performance of the device.

Supplemental static testing was performed (Test #5). This testing involved the measurement of compressive strength properties with the device in a “neutral” position (endplates parallel to each other, or 0°), at maximum flexion (13.5°), and at maximum extension (7.5°). These maximum angles were defined using range of motion data from L4-5 and adding 2 degrees to represent a worst case scenario. Cores of 7.5 mm and 9.5 mm height were tested with parallel and oblique endplates. The minimum yield loads observed are within the range of expected *in vivo* lumbar loads.

Creep testing (Test #3) was performed to evaluate material deformation of the sliding core over a prolonged period of time under continuous compressive loading. The height of the cores was measured before testing, after 50 hours of applied static load, and after an unloaded recovery period of 48 hours. The creep testing showed a worst case permanent core deformation of 0.57 mm at a load of 4 kN.

Cunningham et al<sup>2</sup> performed an *in vitro* biomechanical study (Test #4) to compare the ROM and center of intervertebral rotation of total CHARITÉ Artificial Disc arthroplasty versus intact disc and conventional threaded fusion cages and cages augmented with transpedicular fixation for single-level spinal instrumentation in cadaveric spines.

The CHARITÉ Artificial Disc increased motion to the operative and adjacent levels in flexion/extension, lateral bending, and axial rotation compared to the intact cadaveric spines, although the increase in flexion/extension was minimal (3%). Mean intervertebral segmental translation in flexion/extension was similar for both CHARITÉ reconstructed and intact specimens. Based on flexion-extension radiographs, the intervertebral centers of rotation were in the posterior one-third of the operative and adjacent intervertebral discs for the CHARITÉ Artificial Disc reconstructed and intact spine conditions.

#### Dynamic Testing

In addition to the static testing, dynamic testing was performed to fully characterize the CHARITÉ Artificial Disc. The dynamic testing included evaluations of:

- fatigue strength
- axial compression fatigue
- shear fatigue
- dynamic compression simulation
- hysteresis

Summary results are listed in **Table 7**.

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<sup>2</sup> Cunningham BW, et al. *Biomechanical Evaluation of Total Disc Replacement Arthroplasty: An In Vitro Human Cadaveric Model*. *Spine* 2003; 28:S110-S117.

**Table 7 Summary of Dynamic Tests**

| Test | Test Description                               | Test Samples  | Method   | Results  |
|------|--|---|--|--|
| 1    | Preliminary Axial load Fatigue Testing         | Six 7.5 mm cores with parallel endplates.                           | Test was performed for 10 million cycles at 10 Hz; with 200 N preload in a 37°C water bath and R=10;<br>Two specimens @ 3.77kN peak, two specimens @ 7.5 kN peak, and two specimens @ at 10 kN peak.                         | Endurance limit approximately 3.77 kN to 10 million cycles.  |
| 2    | Supplemental Axial Fatigue Testing             | Five CHARITÉ disc devices with 7.5 mm cores.                        | 10 million cycles at 1 Hz with R=10 in 37°C saline bath; 375 N – 3.75 kN axial load/each device.   | Deformation = 5.9 – 8.8%<br>Mean Deformation = 6.8%<br><br>No gross or catastrophic damage to the core or endplates was observed in tested specimens.  |
| 3    | Supplemental Compressive Shear Fatigue Testing | Five CHARITÉ disc devices with 7.5 mm cores.                        | 10 million cycles at 1 Hz with R=10 in 37°C saline bath; @ 2 kN compressive shear loading.   | Deformation = 3.3 – 7.5%<br>Mean Deformation = 5.2%<br><br>No gross or catastrophic damage to the core or endplates was observed in tested specimens. All of the cores were observed to have a thin layer of white amorphous material on the outer portions of the top and bottom domes. |
| 4    | Dynamic Compression Simulation                 | Ten 7.5 mm cores and ten 9.5 mm cores.                              | 24-hours cyclic loading in 3 phases: 4 hrs @ 0.5Hz, 12 hrs @ 0.017 Hz, 8 hrs @ 0.00028 Hz; 37°C water bath; peak load of 2.5 kN for 5 of each core height; test repeated with peak load of 4.5 kN for 5 of each core height. | Calculated 10-year deformation based on strain data to be less than 8%.<br><br>During 4.5 kN loading, the twisted x-ray wire on the 7.5 mm cores broke.  |
| 5a   | Hysteresis                                     | Five CHARITÉ disc devices with 7.5 mm cores and parallel endplates. | Five sequential axial compressions at 4.2 kN.  | No hysteresis loss was observed in any of the samples.   |
| 5b   |  | Five CHARITÉ disc devices with 7.5 mm cores and parallel endplates. | Five sequential axial compressions at 10.5 kN.   | Hysteresis loss was observed.  |

**Table 7 Summary of Dynamic Tests**

| Test | Test Description | Test Samples   | Method  | Results  |
|------|------------------|--|---|--|
| 5c   |                  | One CHARITÉ disc device with 7.5 mm core and parallel endplates. | Implant placed in L4/5 position of cadaver spine and cycled at 5 Hz and 10 Hz for 20 million cycles with increasing load. | Endplate teeth penetrated vertebral body at 3 kN; bone started to fail at 7.7 kN and endplate subsided into bone at 10.8 kN. |

The fatigue testing was performed using four different test protocols. The first protocol applied a 200 N preload with increasing peak loads at 10 Hz until 10 million cycles or until failure occurred. This study was performed in order to determine the fatigue strength (endurance limit) of a worst-case scenario device. The second and third protocols were performed following the guidelines of the ASTM draft standard "Test Method for Static and Dynamic Characterization of Spinal Artificial Discs." The second test was an axial compression test on five samples using a peak load of 3.75 kN on each sample in a 37°C saline bath for 10 million cycle at a frequency of 1 Hz and R=10. The third test was in a compressive shear loading on five samples using a total peak load of 2 kN in a 37°C saline bath at a frequency of 1 Hz and R=10. A fourth protocol examined the device response to a phased 24-hour cyclic load of 4.5 kN at various frequencies, designed to simulate the *in vivo* loads encountered while walking, sitting, and sleeping.

The fatigue tests showed that the thinnest core remained functional after 10 million cycles at 3.75 kN. Furthermore, the core withstood the simulations of walking, sitting, and bending and lifting weights, even at loads of 4.5 kN, which is within the range of expected *in vivo* lumbar loads.

No gross or catastrophic damage to the core or endplates was observed in tested specimens. However, in Test #3, all of the cores were observed to have a thin layer of white amorphous material on the outer portions of the top and bottom domes, which suggests the potential for wear debris generation.

In test 4, when the 7.5 mm cores were subjected to prolonged periods at 4.5 kN, the resultant deformation broke the twisted x-ray wires. As the central region of the core was compressed, the diameter increased and stressed the x-ray wire. The x-ray wire core was secured such that it had a fixed diameter around the core, and could not expand. Some isolated cases of fractured x-ray wires have been reported clinically. Therefore, the device was modified to minimize the potential for wire fracture by inserting the x-ray wire into the core without fixing the diameter of the wire loop. Rather than completely encircling the core perimeter, the wire has a small gap between its ends so that the wire can flex to accommodate this minor deformation of the core diameter. The wire is still encapsulated within a channel in the core perimeter.

Hysteresis testing showed that at a load of 10.5 kN, even after one cycle, deformation of the core could occur.

#### Wear Testing

Wear testing was performed to characterize the wear behavior of the CHARITÉ Artificial Disc. Three implants were tested in cyclic flexion-extension coupled with axial rotation, and three were

tested in cyclic left-right lateral bending coupled with axial rotation. All implants experienced cyclic compression from 900 N to 1850 N in a heated (37°C) bath of bovine serum solution. Cores were measured and weighed every 200,000 to 300,000 cycles, at which time wear debris samples were collected. Cores were returned to the test constructs each time in different orientations. The test was performed to 10 million cycles.

The test samples showed an average wear rate of 0.11 mg per million cycles for a total average wear of 1.1 mg over 10 million cycles. The total height loss (UHMWPE core creep) after testing was 0.2 mm  $\pm$  0.02 mm. Analysis of the wear debris showed that 52-100% of the particles observed were sub-micron particles. Particle morphologies tended to be flake-like in earlier cycles and globular/granular in later cycles. The median diameter of the particles was approximately 0.2 microns, with sizes from 0.08 to 16.3 microns.

The results from the wear study suggest that the device will generate wear debris at expected lumbar loads. The evaluation of such wear debris was conducted in animal studies.

#### Biocompatibility Studies

The endplates are constructed of CoCrMo alloy that conforms to ISO 5832-4 and ASTM F-75. The wire consists of CoCrMo alloy that conforms to ISO 5832-7 and ASTM F-1058. The UHMWPE core conforms to ISO 5834-2 and ASTM F-648. These materials have a long history of use in medical implants with no significant biocompatibility issues.

To further characterize the biological response to the implant and wear debris, a biological reaction study was performed using UHMWPE particulate in a rabbit model. When analyzed by volume, 95% of this particulate was shown to be less than or equal to 5 microns in diameter. An analysis based on the number of particles demonstrated that 50% of the particles were less than 1 micron in diameter and 90% were less than 3 microns in diameter.

In addition, the particulate used in the rabbit study was delivered as an acute dose of 3 mg in a 5 kg rabbit. The dose was applied directly to the dura. This represents a worst-case scenario analogous to acutely delivering 42 mg of UHMWPE wear debris in a 70 kg individual, or more than 30 times the average amount of wear debris generated during 10 million cycles of the *in vitro* wear testing.

Six months after implantation in the rabbit, there was no evidence of an acute neural or systemic histopathologic response to the UHMWPE debris. There was a chronic histiocytic reaction localized primarily within the epidural fibrous layers, but there was no cell apoptosis.

#### Animal Studies

Cunningham et al. implanted a porous-coated version of the CHARITÉ Artificial Disc in mature baboons<sup>3</sup>. The study investigated the biological responses to the device and evaluated and compared its mechanical characteristics pre- and post- implantation. Using an *in vivo* non-human primate model, the primary objectives of this pre-clinical animal study are as follows:

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<sup>3</sup> Cunningham BW, Dmitriev AE, Hu N, McAfee PC; General principles of total disc replacement arthroplasty: seventeen cases in a nonhuman primate model, *Spine*. 2003 Oct 15; 28(20):S118-24.

- Assess the histopathologic response in local and systemic tissues to prosthesis disc material and possibly wear debris generated.
- Characterize stiffness properties from normal range of motion and compare it to an instrumented segment with the CHARITÉ Disc.

At 6 months after surgery, the range of motion exhibited by subjects implanted with the porous-coated version of the CHARITÉ Artificial Disc and the non-operative control subjects under axial compression, flexion/extension, and lateral bending showed no statistical difference compared to intact primate spinal segments. Histochemical assays showed no accumulation of particulate wear debris (no titanium, ultra high molecular weight polyethylene, or cobalt-chrome) or cytokines (tumor necrosis factor-alpha, prostaglandin E2, interleukin-1, -2, or -6).

## **X. SUMMARY OF CLINICAL STUDIES**

### Study Objectives

Clinical data were collected to evaluate the safety and effectiveness of the CHARITÉ Artificial Disc as compared to the control device (a commercially available interbody fusion system). The purpose of the study was to demonstrate the non-inferiority of the CHARITÉ Artificial Disc to an interbody fusion system.

### Study Design

A multi-center, prospective, randomized, controlled study was conducted consisting of subjects with single-level DDD of the lumbar spine (L4/L5 or L5/S1) who had not previously received surgical treatment, except for a prior discectomy, laminotomy/ectomy, or nucleolysis at the same level, and have failed to improve with conservative treatment for at least 6 months prior to enrollment. Subjects were randomized to receive either the CHARITÉ Artificial Disc or an anterior lumbar interbody fusion using the control. Prior to randomization of the study subjects, the first five subjects enrolled at each investigational site were implanted with the CHARITÉ Artificial Disc for the purpose of surgeon training. Subjects were randomized in a two to one ratio of CHARITÉ Artificial Disc recipients to control recipients. Blocking techniques (fixed block size of 6, randomized computer-generated sequence, concealment of treatment assignments using sealed envelopes, etc.) were used to ensure a balance between the treatment groups at each center.

All subjects randomized to receive the CHARITÉ Artificial Disc first underwent discectomy to remove the damaged disc and were implanted with the device in the same procedure (no other instrumentation was used to secure the device in position). The interbody fusion group was used as the control group for this study. Subjects randomized to the control group were implanted with the control packed with iliac crest autograft bone.

All implants for the study were performed anteriorly to ensure comparability between the two treatment arms.

Safety and effectiveness was assessed in all randomized subjects. An individual subject was considered a study success (i.e., Overall Success) if all of the following conditions were met:

- improvement in the Oswestry Disability Index (ODI)  $\geq 25\%$  at 24 months compared to the score at baseline
- no device failures requiring revision, re-operation, or removal
- absence of major complications, defined as major blood vessel injury, neurological damage, or nerve root injury
- maintenance or improvement in neurological status at 24 months, with no new permanent neurological deficits compared to baseline

The sponsor considered the study a success if the Overall Success rates of the two treatment groups were non-inferior, i.e., the difference in Overall Success rates (i.e., non-inferiority margin) is no greater than 15%. However, FDA requested that the data also be analyzed and reported using: 1) an improvement in the ODI  $\geq 15$  points at 24 months compared to the score at baseline; and 2) a non-inferiority margin of 10%.

#### Inclusion/Exclusion criteria

To qualify for enrollment in the study, subjects met all the inclusion criteria and none of the exclusion criteria listed in the following table:

| Inclusion   | Exclusion   |
|---|---|
| <ul style="list-style-type: none"> <li>• Male or female</li> <li>• Age 18-60 years</li> <li>• Symptomatic degenerative disc disease with objective evidence of lumbar DDD by CT or MR scan, followed by discogram</li> <li>• Single level disease at L<sub>4</sub>L<sub>5</sub> or L<sub>5</sub>S<sub>1</sub></li> <li>• Minimum of 6 months of unsuccessful conservative treatment</li> <li>• Oswestry Low Back Pain Disability Questionnaire <math>\geq 30</math> points</li> <li>• Patient a surgical candidate for an anterior approach to the lumbar spine (&lt;3 abdominal surgeries)</li> <li>• Back pain at the operative level only (by discogram)</li> <li>• Leg pain and/or back pain in the absence of nerve root compression, per MRI or CT scan, without prolapse or narrowing of the lateral recess.</li> <li>• VAS <math>\geq 40</math>mm</li> <li>• Able to comply with protocol</li> <li>• Informed consent</li> </ul> <p>DDD is defined as discogenic back pain with degeneration of the disc as confirmed by history and radiographic studies with one or more of the following factors:</p> <ul style="list-style-type: none"> <li>◦ Contained herniated nucleus pulposus</li> <li>◦ Facet joint degeneration/changes</li> <li>◦ Decreased disc height by <math>\geq 2</math>mm, and/or</li> <li>◦ Scarring/thickening of ligamentum flavum, annulus fibrosus, or facet joint capsule</li> </ul> | <ul style="list-style-type: none"> <li>• Previous or other spinal surgery at any level, except prior discectomy, laminotomy, laminectomy, or nucleolysis at the same level</li> <li>• Multiple level degeneration</li> <li>• Previous trauma to the L<sub>4</sub>, L<sub>5</sub>, or S<sub>1</sub> levels in compression or burst</li> <li>• Non-contained or extruded herniated nucleus pulposus</li> <li>• Mid-sagittal stenosis of &lt;8mm (by CT or MR)</li> <li>• Spondylolisthesis &gt;3mm</li> <li>• Lumbar scoliosis (&gt;11° sagittal plane deformity)</li> <li>• Spinal tumor</li> <li>• Active systemic or surgical site infection</li> <li>• Facet joint arthrosis</li> <li>• Arachnoiditis</li> <li>• Isthmic spondylolisthesis</li> <li>• Chronic steroid use</li> <li>• Metal allergy</li> <li>• Pregnancy</li> <li>• Autoimmune disorders</li> <li>• Psychosocial disorders</li> <li>• Morbid obesity (BMI &gt;40)</li> <li>• Bone growth stimulator use in spine</li> <li>• Investigational drug or device use within 30 days</li> <li>• Osteoporosis or osteopenia or metabolic bone disease</li> <li>• Positive single or bilateral straight leg raising test</li> </ul> |

### Post-operative care

Following surgery, subjects in both treatment groups received treatment according to the same standardized, post-operative care protocol. Subjects were permitted to ambulate on the day of surgery, as tolerated, with an elastic bandage or lumbosacral orthosis (LSO) to provide support to the abdominal musculature. Lumbar stabilization therapy was initiated 2-4 weeks post-operatively as tolerated. Water therapy and/or swimming were encouraged and could begin two weeks post-operatively. Aerobic walking was stressed for the first six post-operative weeks with more resistive exercises using fitness machines after that period. Subjects were instructed not to engage in activities that required lifting, bending or twisting for six months following surgery.

### Clinical and radiographic effectiveness parameters

Subjects were evaluated preoperatively, intra-operatively, and immediately postoperatively, then at 6-weeks, 3, 6, 12 and 24-months. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial.

Overall Success was determined from data collected during the initial 24 months of follow-up. Primary outcome parameters were evaluated for all treated subjects at 6, 12 and 24 months using both the sponsor's protocol-defined success criteria and FDA's definition of overall success as described above. The primary clinical parameters assessed were of function (improvement of at least 25% in ODI Score [sponsor's criteria] or 15 points in the ODI score [FDA's criteria] at 24-months compared to baseline), maintenance or improvement in neurological status at 24-months with no permanent neurological deficits compared to baseline status, absence of major complications defined as clinically significant vessel injury, neurological damage or nerve root injury, and no device failures requiring revision, re-operation or removal.

Neurological status was a global assessment that incorporated information from the following: (i) reflexes at the knee and ankle (absent/present, symmetrical/asymmetrical); (ii) motor function (bilateral or unilateral weakness, evaluated on a 5-point scale for gluteus maximus, iliopsoas, quadriceps, hamstrings, anterior tibial group, posterior tibial, extensor hallucis longus, and flexor hallucis); (iii) sensitivity to light touch (numbness, tingling in the groin, anterior thigh, medial leg, lateral leg, and lateral foot); (iv) strength of lower extremities; and (v) straight leg raise, with evaluation of cross-positive reactions.

The secondary endpoints assessed were Quality of Life measured with the Short Form-36 or SF-36 questionnaire (improvement of 15% in the Physical Composite Score (PCS) and Mental Composite Score (MCS) at 24-months compared to baseline), improvement in pain by 20mm or more on a Visual Analog Scale comparing baseline to 24-month post-operative score, disc height (measured by standard lateral radiograph) with only changes  $\geq 3$ mm considered significant, displacement or migration of the device (only changes  $\geq 3$ mm considered significant) and no significant radiolucency for the Charité Disc at 24-months when compared to post-operative films.

Other outcomes measured included length of hospital stay, patient satisfaction, and range of motion in flexion/extension.

For fusion assessment in either group, the anterior/posterior, lateral and flexion/extension x-rays were evaluated using the following criteria:

- Translational motion <3mm
- Angular motion <5°
- Absence of radiolucent lines around <50% of the assembly

Radiographs were used to monitor the occurrence of some of the adverse events and complications, including subsidence of the device into the adjacent disc or other changes in the implant and spinal instability.

#### Subject Demographics and Accountability

Fifteen (15) sites participated in the study with a planned total of three hundred sixty-six (366) subjects enrolled; the first five subjects at each center were not randomized and served as training patients for the CHARITÉ Artificial Disc. At 24 months, 205 subjects were enrolled in the treatment arm and received the CHARITÉ Artificial Disc and 99 subjects were enrolled in the control group and received the control.

Table 9 below shows the demographics and baseline characteristics of the investigational and control groups.

**Table 9 Demographics and Baseline Characteristics**

| Characteristic                              | CHARITÉ     | Control     | P-value* |
|---|-------------|-------------|----------|
| Number of subjects enrolled                 | 205         | 99          |          |
| Gender                                      |             |             |          |
| Female                                      | 113 (55%)   | 44 (44%)    | 0.0875   |
| Male  | 92 (45%)    | 55 (56%)    |          |
| Race  |             |             |          |
| Caucasian                                   | 188 (92%)   | 87 (88%)    | 0.5402   |
| African American                            | 8 (4%)      | 5 (5%)      |          |
| Other                                       | 9 (4%)      | 7 (7%)      |          |
| Age (years)                                 |             |             |          |
| Mean (Std)                                  | 39.6 (8.16) | 39.6 (9.07) | 0.9455   |
| Median                                      | 40.0        | 39.0        |          |
| Min, Max                                    | 19, 60      | 20, 60      |          |
| Age categories                              |             |             |          |
| >45 Years                                   | 47 (23%)    | 30 (30%)    | 0.2051   |
| ≤45 Years                                   | 158 (77%)   | 39 (70%)    |          |
| Body Mass Index                             |             |             |          |
| Mean (Std)                                  | 26.0 (4.23) | 27.0 (4.76) | 0.0557   |
| Median                                      | 26.0        | 26.9        |          |
| Min, Max                                    | 17, 39      | 18, 40      |          |
| Targeted level of disc disease at screening |             |             |          |
| L4/L5                                       | 61 (30%)    | 32 (32%)    | 0.6910   |
| L5/S1                                       | 144 (70%)   | 67 (68%)    |          |
| Pre-operative activity level                |             |             |          |
| Active                                      | 9 (4%)      | 1 (1%)      | 0.0635   |
| Moderate                                    | 26 (13%)    | 5 (5%)      |          |
| Light                                       | 54 (26%)    | 27 (27%)    |          |
| Minimal                                     | 116 (57%)   | 66 (67%)    |          |

\*Fisher's exact test was used to test categorical variables and a t-test was used to test means.

The numbers shown in Table 10 below represent all randomized subjects who completed all evaluations at each time point within the windows defined in the approved investigational protocol.

**Table 10 Patient Accountability**

|                   | Post-op |         | 6 wks   |         | 3 mo    |         | 6 mo    |         | 12 mo   |         | 24 mo   |         |
|-------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Patients          | Charité | Control | Charité | Control | Charité | Control | Charité | Control | Charité | Control | Charité | Control |
| Theoretically due | 205     | 99      | 205     | 99      | 205     | 99      | 205     | 99      | 205     | 99      | 205     | 96      |
| Deaths            | 1       | 0       | 1       | 0       | 1       | 0       | 1       | 0       | 1       | 0       | 1       | 0       |
| Failures          | 3       | 1       | 3       | 1       | 3       | 1       | 3       | 1       | 7       | 4       | 12      | 8       |
| Withdrawn         | 0       | 0       | 0       | 1       | 0       | 2       | 0       | 4       | 5       | 9       | 16      | 17      |
| Expected          | 201     | 98      | 201     | 97      | 201     | 96      | 201     | 94      | 192     | 86      | 176     | 74      |
| Missed            | 2       | 1       | 4       | 1       | 11      | 2       | 12      | 5       | 8       | 5       | 15      | 8       |
| Actual            | 199     | 97      | 197     | 96      | 190     | 94      | 189     | 89      | 184     | 81      | 161     | 66      |
| % follow-up       | 99.0    | 99.0    | 98.0    | 99.0    | 94.5    | 97.9    | 94.0    | 94.7    | 95.8    | 94.2    | 91.5    | 89.2    |

An analysis was performed to assess the ability to pool data across sites and to compare data across the study arms. These analyses evaluated the primary clinical outcome variables, as well as overall success, and found no differences that would prevent pooling of the data across the sites within a given group of subjects.

#### Surgical Results and Hospitalization

All implant surgeries for the study were performed anteriorly to ensure comparability between the two treatment arms. While not statistically significant, the operative time and mean blood loss for the subjects who received the CHARITÉ Artificial Disc were lower than for the control group. Subjects who received the CHARITÉ Artificial Disc were discharged from the hospital on average in 3.7 days compared to 4.2 days in control subjects.

**Table 11 Surgical Procedure and Hospitalization**

| Characteristic              | CHARITÉ        | Control        |
|-----------------------------|----------------|----------------|
| Number of subjects enrolled | 205            | 99             |
| Level fused or implanted    |                |                |
| L4/L5                       | 61 (30%)       | 32 (32%)       |
| L5/S1                       | 144 (70%)      | 67 (68%)       |
| Total surgery time (min)    |                |                |
| Mean (Std)                  | 110.8 (47.66)  | 114.0 (67.85)  |
| Median                      | 99.0           | 87.0           |
| Min, Max                    | 42.0, 300.0    | 40.0, 410.0    |
| Estimated blood loss (cc)   |                |                |
| N                           | 200            | 99             |
| Mean (Std)                  | 205.0 (211.70) | 208.9 (283.95) |
| Median                      | 150.0          | 100.0          |
| Min, Max                    | 10.0, 1500.0   | 20.0, 2000.0   |
| Duration of Hospitalization |                |                |
| N                           | 204            | 99             |
| Mean                        | 3.7            | 4.2            |
| Std. Dev.                   | 1.18           | 1.99           |
| Median                      | 4.0            | 4.0            |
| Min, Max                    | 1.0, 11        | 2.0, 16        |

### Clinical effectiveness evaluation

The primary effectiveness endpoint of this study was the difference in proportion of Overall Success between the two treatment groups. The success status of subjects was summarized by treatment group using counts and percentages. Table 12 below compares the success rates for the individual primary outcome parameters for all randomized subjects as well as the Overall Success rates, using both the sponsor's and FDA's ODI success criteria. Primary endpoint data were collected and analyzed 24-months after surgery.

The analysis population which was used to assess these endpoints consisted of all randomized subjects who completed all evaluations at the 24-month time point, regardless of when the 24-month measurements occurred.

**Table 12 Comparison of Success Rates for Efficacy at 24 Months**

| Characteristic                          | 25% Improvement |          | 15-point Improvement |          |
|---|-----------------|----------|----------------------|----------|
|   | Charité         | Control  | Charité              | Control  |
| Number of subjects (completers)         | 184             | 81       | 184                  | 81       |
| Oswestry score from baseline            |                 |          |                      |          |
| Success                                 | 130 (71%)       | 50 (62%) | 117 (64%)            | 47 (58%) |
| Device failures <sup>1</sup>            |                 |          |                      |          |
| Success                                 | 175 (95%)       | 74 (91%) | 175 (95%)            | 74 (91%) |
| Major complications <sup>2</sup>        |                 |          |                      |          |
| Success                                 | 182 (99%)       | 80 (99%) | 182 (99%)            | 80 (99%) |
| Neurological deterioration <sup>3</sup> |                 |          |                      |          |
| Success                                 | 167 (91%)       | 77 (95%) | 167 (91%)            | 77 (95%) |
| Overall Success Rate                    | 117 (64%)       | 46 (57%) | 107 (58%)            | 44 (54%) |

<sup>1</sup> Device failures requiring revision, reoperation, or removal.

<sup>2</sup> Major complications defined as major vessel injury, neurological damage, nerve root injury, or death.

<sup>3</sup> Slight deterioration, significant deterioration, or mixed response at 24 months.

The two-sided 90% confidence interval indicates that the overall success rate for the CHARITÉ Artificial Disc is not worse than the control rate by more than 10%, regardless of which set of study success criteria is used.

Secondary endpoints comprised measurements of:

- components of the primary endpoints (ODI and neurological scores)
- pain, using a visual analog scale (VAS)
- quality of life, using the Short Form-36 Questionnaire (SF-36)
- disc height, using a standard lateral radiograph
- migration of the device
- radiolucency for CHARITÉ Artificial Disc subjects

All of the results from the secondary endpoints at 24 months indicate the non-inferiority of the CHARITÉ Artificial Disc group to the control group.

Mean ODI scores at baseline were similar for the two treatment groups: 50.6 for the CHARITÉ Artificial Disc group and 52.1 in the control group. Mean scores post-operatively were 37.7, 29.9,

27.5, 26.0, and 26.3 at 6 week, 3 month, 6 month, 12 month and 24 months respectively for the CHARITÉ group and 43.7, 37.4, 35.8, 31.8, and 30.5 for the same time intervals in the control group. A decrease in ODI score compared with baseline indicates improvement.

Mean VAS pain scores at baseline were similar for the two treatment groups: 72.0 in the CHARITÉ Artificial Disc subjects and 71.8 in the control subjects. At 24 months, these mean scores had dropped to 31.2 and 37.5, respectively. A decreased score compared to the baseline score indicates an improvement.

Results of Quality of Life assessments (SF-36) are used to assess physical and mental well-being. The SF-36 Physical Composite Score (PCS) has been shown to be valid as a physical health measure. The SF-36 (MCS) is a composite of the Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH) scales and is less appropriate as an outcome measurement in surgical studies.

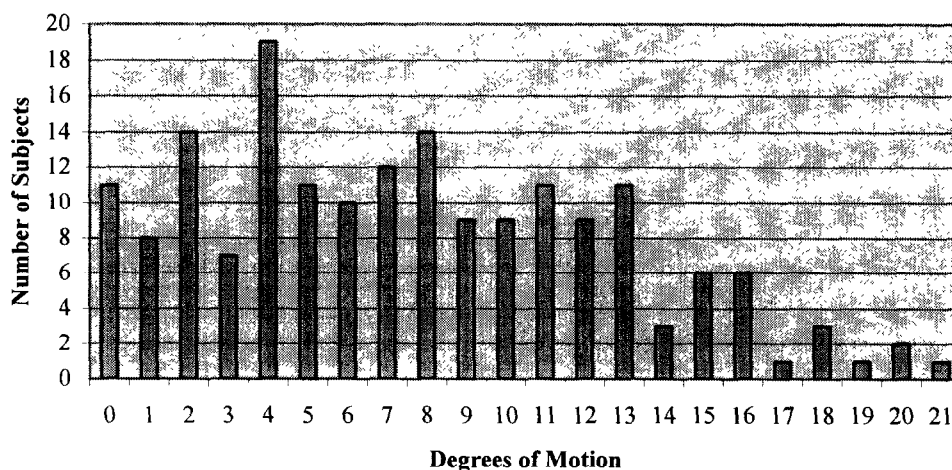
After the 3 month visit, for both treatment groups there is an improvement compared to baseline for the Physical Composite Score (PCS) and Mental Component Score (MCS). At 24 months, the percentage of CHARITÉ Artificial Disc subjects who had a 15% improvement from baseline in the PCS score was 72%, compared with 63% for the control subjects. For the MCS score, the percentages were 50% and 51%, respectively. Note that an increasing score designates improvement in these measures.

Radiographic measurements of disc height showed a low rate of disc space height loss in both treatment groups. In subjects treated with the CHARITÉ Artificial Disc, mean preoperative disc height was 5.7 mm and mean disc heights were 13.2, 13.1, 13.0, and 12.9 mm at 3, 6, 12, and 24 months, respectively. In subjects treated with the control device, mean preoperative disc height was 6.3 mm and mean disc heights were 11.5, 11.4, 11.1, and 10.7 mm at 3, 6, 12, and 24 months, respectively.

Vertebral range of motion (ROM) in degrees at the operative level, determined as the difference in Cobb measurements between dynamic flexion/extension lateral radiographs, was determined at 3, 6, 12 and 24 months. Mean ROM for CHARITÉ Artificial Disc subjects was 5.0, 6.1, 6.9, and 7.5 degrees at 3, 6, 12, and 24 months, respectively. Mean ROM for control subjects was 2.4, 2.1, 1.5, and 1.1 degrees at 3, 6, 12, and 24 months, respectively.

FDA requested that the sponsor provide a histogram showing the range of ROM values recorded for all randomized CHARITÉ Artificial Disc subjects at 24 months. This histogram used values obtained by rounding recorded ROM for each subject to the nearest integer.

**Figure 1 Histogram of CHARITÉ ROM at 24 Months**



FDA also analyzed ROM data versus Overall Success outcomes for all CHARITÉ Artificial Disc subjects with available ROM data at 24 months. No statistically significant association was found between ROM and success/failure at 24 months.

Identification of radiolucency and longitudinal ossification was completed for CHARITÉ Artificial Disc subjects only. Radiolucency was identified for 1 (1%) subject at 12 months and 2 (1%) subjects at 24 months. Longitudinal ossification was identified for 1 (1%), 3 (2%), 7 (4%) and 11 (6%) subjects at 6 weeks, 6 months, 12 months and 24 months, respectively.

## **XI. CONCLUSIONS DRAWN FROM THE STUDIES**

The valid scientific evidence presented in the preceding sections demonstrates that the CHARITÉ Artificial Disc is safe and effective in the treatment of DDD at one level in the L4-S1 region of the lumbar spine; and the device is non-inferior when comparing Overall Success rates to the control in treatment of DDD at one level (L4-S1).

## **XII. PANEL RECOMMENDATION**

The PMA for the CHARITÉ Artificial Disc was reviewed at the Orthopaedic and Rehabilitation Devices Advisory Panel meeting held on June 2, 2004. The Panel recommended to the FDA that the PMA be approved subject to the following conditions:

1. A postmarket study of all patients enrolled in the IDE study (including continued access patients) should be followed until the last-enrolled continued access subject reaches the two-year time point. The follow-up data from all these subjects should be provided to FDA.

2. All patients who are treated with the CHARITÉ Artificial Disc should be provided with documentation describing the specific components of their implant, including associated lot numbers, as well as a telephone number to be used for the reporting of any adverse events.
3. A post market *in vitro* study to further assess wear debris. Wear debris testing should be conducted utilizing a combination of flexion/extension (FE) and lateral bending (LB) motions (without axial rotation) to determine if this combination would produce a different wear profile.
4. FDA should consider required surgeon training.
5. The FDA and the sponsor should discuss the following conditions of approval to come to a mutually agreeable course of action. This discussion will consider whether each items should be addressed pre- or post-market:
  - a. Provide mobility testing data or complete references.
  - b. Provide an adequate rationale for “normal biomechanics” including demonstration that facet joint strains/stresses are comparable to the control group patients.
  - c. Provide an adequate rationale for not testing the biological response to submicron particles of ultra high molecular weight polyethylene.
  - d. Clarify the neurological grading scale and how statistics were applied to this measure.
  - e. Stratify results by indication group, particularly for patients with facet joint changes noted in preoperative assessments, for both the investigational and control groups.
  - f. For those investigational patients with range of motion in the zero to five degrees range at the two-year time point, consider these subjects as failures, and reevaluate the study data.
  - g. Consider if axial imaging can be done to compare facet degeneration at the index level at the 24-month time point and preoperatively.
  - h. Provide radiographic evaluation of adjacent segment degeneration for the preoperative and 24-month time points, as well as through the follow-up period described in Condition #1.

### **XIII. CDRH DECISION**

FDA concurred with the Panel’s recommendation for approval. FDA concurred with the Panel regarding the need for a post-approval study to collect long-term safety and effectiveness data, the need for documentation of the patient’s specific implantation information, and the need for surgeon training.

FDA did not agree with the need for additional wear debris testing using a combination of flexion/extension (FE) and lateral bending (LB) motions. The wear debris testing conducted utilized a methodology whereby the UHMWPE cores were randomly reoriented every 200,000 to 300,000 cycles during visual inspections of the tested implants. Because the cores are symmetric, it is believed that the reorientations would produce cross-wear similar to a test conducted with combined FE/LB motions.

FDA believed Items 5a, 5c, and 5d should be addressed premarket. These items were resolved with the data presented in the sponsor's PMA. FDA believed Items 5b, 5e, 5g, and 5h could not be addressed premarket because the clinical study was not designed to evaluate adjacent spinal segments and therefore no data were collected to address these issues. However, these items could be addressed through data collected as part of a post-approval study, except for evaluation of facet joint strains/stresses.

FDA did not agree that the data should be reanalyzed by treating investigational subjects with measured range of motion in the zero to five degrees range as failures (Item 5f). The study was not designed to evaluate range of motion as part of the definition of study success.

In order to gather long-term safety and effectiveness data, the sponsor has proposed to conduct a post-approval study to obtain a total of five-year follow-up data from all randomized subjects in the clinical study. The study will utilize the same endpoints as the clinical study. The post-approval study will also evaluate adjacent segment degeneration and the correlation of range of motion data with ODI and VAS scores. Because of the unknown long-term device performance, the post-approval study will include analysis of any retrieved implants returned to the sponsor.

FDA worked with the sponsor to review the content of the training program, finalize product labeling, and to finalize the requirements of the post approval study. The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order on October 26, 2004.

Expedited review status of this PMA was granted on April 4, 2003, because the device may provide added benefits to existing alternatives (e.g., decreased stresses on adjacent vertebral levels and discs, shorter recovery times, etc.).

#### **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See the product labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See the Approval Order.